

The elusive nature of APOE ε4 in mid-adulthood: understanding the cognitive profile

Article (Accepted Version)

Lancaster, Claire, Tabet, Naji and Rusted, Jennifer (2017) The elusive nature of APOE ε4 in mid-adulthood: understanding the cognitive profile. *Journal of International Neuropsychological Society*, 23 (3). pp. 239-253. ISSN 1355-6177

This version is available from Sussex Research Online: <http://sro.sussex.ac.uk/id/eprint/66373/>

This document is made available in accordance with publisher policies and may differ from the published version or from the version of record. If you wish to cite this item you are advised to consult the publisher's version. Please see the URL above for details on accessing the published version.

Copyright and reuse:

Sussex Research Online is a digital repository of the research output of the University.

Copyright and all moral rights to the version of the paper presented here belong to the individual author(s) and/or other copyright owners. To the extent reasonable and practicable, the material made available in SRO has been checked for eligibility before being made available.

Copies of full text items generally can be reproduced, displayed or performed and given to third parties in any format or medium for personal research or study, educational, or not-for-profit purposes without prior permission or charge, provided that the authors, title and full bibliographic details are credited, a hyperlink and/or URL is given for the original metadata page and the content is not changed in any way.

The elusive nature of *APOE* ε4 in mid-adulthood: understanding the cognitive profile

Claire Lancaster

School of Psychology, University of Sussex, Brighton, East Sussex, BN1 9QG
01273 678916
claire.lancaster@sussex.ac.uk

Dr Naji Tabet

Brighton and Sussex Medical School, Institute of Postgraduate Medicine, Brighton, East
Sussex, BN1 9PH
01273 644503

Prof. Jennifer Rusted

School of Psychology, University of Sussex, Brighton, East Sussex, BN1 9QG
01273 678325

Corresponding authors: Claire Lancaster, Jennifer Rusted

Running title: APOE: the cognitive profile in mid-adulthood

Word count: 4733

Abstract

Objective: The *APOE* $\epsilon 4$ allele is an established risk factor for dementia, yet this genetic variant is associated with a mixed cognitive profile across the lifespan. This paper undertakes both a systematic and meta-analytic review of research investigating *APOE*-related differences in cognition in mid-adulthood, when detrimental effects of the allele may first be detectable.

Method: 36 papers investigating the behavioural effects of *APOE* $\epsilon 4$ in mid-adulthood (defined as a mean sample age between 35-60 years) were reviewed. In addition, the effect of carrying an $\epsilon 4$ allele on individual cognitive domains was assessed in separate meta-analyses.

Results: The average effect size of *APOE* $\epsilon 4$ status was non-significant across cognitive domains. Further consideration of genotype effects indicates preclinical effects of *APOE* $\epsilon 4$ may be observable in memory and executive functioning.

Conclusions: The cognitive profile of *APOE* $\epsilon 4$ carriers at mid-age remains elusive. Whilst there is support for comparable performance by $\epsilon 4$ and non- $\epsilon 4$ carriers in the 5th decade, studies administering sensitive cognitive paradigms indicate a more nuanced profile of cognitive differences. Methodological issues in this field preclude strong conclusions, which future research must address, as well as considering the influence of further vulnerability factors on genotype effects.

Keywords: *Cognitive Aging, Middle-aged, Neuroimaging, Alzheimer Disease, Memory, Executive Function*

Introduction

Pathological cognitive ageing is an increasing problem worldwide, with 850,000 cases of Alzheimer's disease (AD) at present in the UK alone. With prevalence expected to double within the next 20 years (Alzheimer's society, 2016), understanding the risk factors associated with dementia is crucial. The Apolipoprotein E (*APOE*) epsilon 4 ($\epsilon 4$) allele is the leading genetic risk factor for late-onset Alzheimer's disease (Corder et al., 1993; Farrer et al., 1997). This variant of the *APOE* gene constitutes one of the three *APOE* alleles ($\epsilon 2$, $\epsilon 3$ and $\epsilon 4$), present in approximately 25% of the population (Mahley, 1988).

Systematic reviews of studies including healthy older adults support an association between possession of an $\epsilon 4$ allele and cognitive impairment in ageing more generally (Small, Rosnick, Fratiglioni, & Bäckman, 2004; Wisdom, Callahan, & Hawkins, 2011), although not all studies are consistent in reporting this effect (Bunce et al., 2014; Bunce, Kivipelto, & Wahlin, 2004; Caselli et al., 2014). The association between $\epsilon 4$ and healthy cognitive ageing suggests the effects of this variant are not solely linked to neuropathology, and so a dimensional approach is needed to consider the overlap between healthy and pathological ageing (Walhovd, Fjell, & Espeseth, 2014). Potentially accounting for inconsistency within the older-adult literature, meta-analyses of study effect sizes suggest *APOE*-related differences are small and limited to certain classes of cognitive task, including global cognition, episodic memory, perceptual speed and executive function (EF) (Small et al., 2004; Wisdom et al., 2011). Age and gene-dose are also implicated as important moderators of $\epsilon 4$ effects (Small et al., 2004). These factors are important for how we approach understanding *APOE* genotype differences.

Curiously, the detrimental effects of *APOE* $\epsilon 4$ are not consistent across the lifespan, muddying attempts to explain the causality of this risk factor for decline. In naturalistic research, $\epsilon 4$ carriers (henceforth $\epsilon 4+$) were reported to have higher IQ and greater educational achievement than $\epsilon 4$ non-carriers (henceforth $\epsilon 4-$) (Hubacek et al., 2001; Yu, Lin, Chen,

Hong, & Tsai, 2000). This led to the hypothesis that $\epsilon 4+$ may show cognitive advantages earlier in life, with performance advantages similarly being demonstrated in some (Alexander et al., 2007; Han et al., 2007; Schultz et al., 2008), although not all (Bunce et al., 2014; Bunce, Anstey, Burns, Christensen, & Easteal, 2011; Jorm et al., 2007) studies assessing genotype differences with neuropsychological batteries. Importantly, no steps have been taken to explore the potential moderating effects of early-life IQ and education on the trajectory of cognitive ageing in $\epsilon 4+$ through longitudinal research.

A meta-analytic review found no conclusive support for an $\epsilon 4+$ advantage in younger years (Ihle, Bunce, & Kliegel, 2012); however, the authors acknowledge conclusions may stem from the predominant inclusion of studies using quick to administer behavioural assessments. Such assessments are typically used for detecting clinically relevant cognitive differences rather than the subtle changes expected in young healthy adults. When considering evidence from research paradigms designed to sensitively index select cognitive processes, $\epsilon 4+$ advantages have been reported. Young $\epsilon 4+$ showed behavioural advantages compared to $\epsilon 4-$ on a delayed episodic memory measure (Mondadori et al., 2007). Furthermore, Marchant, King, Tabet, & Rusted (2010) demonstrated an $\epsilon 4+$ advantage in 18-30 year olds across a number of domains including prospective memory, decision-making and sustained attention. Advantages in sustained attention were replicated in a further study (Rusted et al., 2013), which also reported $\epsilon 4+$ advantages in covert attention (Rusted et al., 2013). In addition, $\epsilon 4+$ show EF advantages up until age 50 (Taylor et al., 2016). While carrying an $\epsilon 4$ allele might promote cognitive advantages in youth, it is important to understand how early differences cumulatively impact on the ageing trajectory of $\epsilon 4+$.

This review attempts to unravel the development of *APOE* $\epsilon 4$ cognitive effects by considering studies recruiting healthy mid-age volunteers. Mid-adulthood, as well as being influenced by the cumulative impact of *APOE* $\epsilon 4$ in younger years, may represent a stage when the detrimental effects of carrying this gene are first appearing. Additionally, mid-

adulthood represents a period of emergence for further risk factors for dementia (e.g. declining vascular health), which may modulate the trajectory of cognitive ageing. By studying the impact of risk factors for cognitive decline during mid-adulthood, there is the potential to facilitate the early identification and prevention of cognitive decline. In combination, these motivations emphasise the theoretical interest of studying the effects of *APOE* $\epsilon 4$ at mid-age.

Here, we present a systematic review of research investigating *APOE* differences in mid-adulthood, including studies administering neuropsychological assessment measures, process-specific paradigms, and those assessing change in cognition over time. In addition, $\epsilon 4$ differences in individual cognitive domains are subject to a meta-analytic review.

Methods

Selection of studies

This review was conducted in accordance with the Helsinki declaration. A literature search of 3 databases (PsychInfo, Web of Science and Scopus) was conducted, using search terms including '*APOE*', 'Apolipoprotein', 'cognitive', 'cognition', and 'performance' ¹. The search was limited to articles published post-1993 as this was when the link between *APOE* and detrimental cognitive ageing was first identified (Corder et al., 1993). Articles referenced by included papers were also considered if they aligned with the search criteria of this review. The last update for the search was conducted in July 2016. An overview of the search procedure is given in Figure 1.

¹ The exact search terms were as follows: (Apolipoprotein E OR apoe OR Apolipoprotein-E) AND (Cognition OR Behaviour OR Memory OR Performance OR Executive OR Attention OR Mid-age OR Adult OR Mid-adulthood). These key words must be found in the title or abstract of identified papers.

Eligibility criteria

Studies were included in the review if they met the following criteria: (1) The study included volunteers grouped by *APOE* genotype, enabling the comparison of $\epsilon 4+$ to an $\epsilon 4-$ group. (2) The mean age of volunteers in the study falls between 35-60 years. If no mean was available, the entire age range included must fall within 35-60 years. (3) The study included cognitively healthy adult volunteers. Studies including clinical groups, for example diagnosed with dementia, neural trauma or a psychiatric condition were excluded. (4) At least one objective measure of cognition must be included. (5) The study was published in English. In some cases, studies overlapped in reporting cognitive performance of the same sample, and so some papers were omitted from the review (e.g. Caselli, Chen, Lee, Alexander, & Reiman, 2008; Zuelsdorff et al., 2013).

Papers were included in the meta-analytic review if sufficient statistical data was provided for calculating the standardised effect size of carrying an $\epsilon 4$ allele on cognitive performance (mean, standard deviation (sd)) compared to an $\epsilon 4-$ group. Study outcomes were included if task performance could be summarised by a measure of accuracy. Authors were contacted where insufficient data was provided.

[INSERT FIGURE 1]

Organisation of studies

36 studies met criteria for being included in this review, 23 of which were included in the meta-analysis. Separate meta-analyses were completed for performance in 7 cognitive domains (global cognition, memory, executive abilities, verbal fluency, language, visuospatial

processing and processing speed). For the narrative review, studies were considered more broadly as those using neuropsychological assessment measures, those that administered more detailed research paradigms and longitudinal assessments.

Statistical analysis

For the outcome of each task included in the meta-analytic review, Hedge's d was calculated as the difference in mean performance between $\epsilon 4+$ and $\epsilon 4-$, divided by the pooled sd. The unbiased estimate (Hedge's g) was used in the analysis, with a positive effect size indicating stronger performance by the $\epsilon 4+$ group. In studies reporting multiple performance outcomes per cognitive domain, effect sizes were averaged across tasks (Borenstein, Hedges, Higgins, & Rothstein, 2009; De Costa, 2009) to prevent the overall effect size for any cognitive domain being over-biased by one sample. Multiple effect sizes were included when studies included more than one sample of $\epsilon 4+$ and $\epsilon 4-$ grouped by another variable such as ethnicity or age (e.g. Blair et al., 2005; Shin et al., 2014). For each domain, a random-effects meta-analysis was completed. Tests of homogeneity were completed for each domain (Q , and I^2) to check the validity of the model. A significant Q statistic indicates a non-homogenous distribution of effect sizes. The I^2 was used to further validate this statistic, as it is not dependent on the number of studies included. Where heterogeneity was detected, data was screened for outliers based on the standardised weight of residuals and the difference excluding a study made to heterogeneity.

Results

Table 1 presents a summary of cross-sectional studies included in this review, including details of the sample demographics and cognitive tasks administered. A further

summary of the studies included in each meta-analysis and the associated effect sizes are shown in Table 2.

[INSERT TABLE 1]

[INSERT TABLE 2]

Meta-analyses

A summary of the results from each meta-analytic model is provided in Table 3. Forest plots demonstrating the distribution of effect sizes per domain are shown in Figure 2.

Global

A meta-analysis of effect sizes from 9 studies assessing global cognition found carrying an $\epsilon 4$ allele had a non-significant effect on performance, $d=.03$, $p>.05$. Tests for homogeneity indicated moderate heterogeneity in the individual studies' effect sizes, $Q(8)=15.88$, $p=.044$, $I^2=48.36\%$. Data was screened for outliers, with a sample aged 55-64 years (Shin et al., 2014) identified as substantially increasing heterogeneity. With this effect size removed, carrying an $\epsilon 4$ allele had a positive effect on global cognitive performance in mid-adulthood, with the effect size approaching significance, $d=.09$, $p=.066$ ($Q(7)=5.20$, $p>.05$, $I^2=0\%$).

Memory

Effect sizes from 20 studies were included in a meta-analysis of *APOE* $\epsilon 4$ effects on memory; $\epsilon 4+$ status had a non-significant effect on performance ($d=-.01$, $p>.05$). Again, there was moderate heterogeneity in the sample of effect sizes, $Q(19)=48.38$, $p<.001$, $I^2=10\%$.

After screening for outliers the effect size from Levy et al., (2004) was removed, but the average effect size remained non-significant ($d=-.01, p>.05$)($Q(18)=17.40, p>.05, I^2=0\%$).

Executive abilities

Effect sizes from 12 studies were included in a meta-analysis of *APOE* $\epsilon 4$ effects on executive skills. $\epsilon 4+$ status did not significantly influence performance ($d=-.03, p>.05$). There was no significant heterogeneity in this collection of effect sizes, $Q(11)=8.60, p>.05, I^2=0\%$.

Verbal fluency

10 studies contributed effect sizes to a meta-analysis of $\epsilon 4+$ effects on fluency performance. The average effect of *APOE* genotype was non-significant ($d=.02, p>.05$). There was no significant heterogeneity in this sample of effect sizes, $Q(9)=8.17, p>.05, I^2=21.25\%$.

Language

Effect sizes from 8 studies were included in a meta-analysis which found no significant effect of carrying an $\epsilon 4$ allele on language performance ($d=.00, p>.05$). There was no significant heterogeneity in this sample of effect sizes, $Q(7)=6.81, p>.05, I^2=26.65\%$.

Visuospatial

Effect sizes from 5 studies were included in the meta-analysis. There was no significant effect of carrying an $\epsilon 4$ allele on visuospatial performance ($d=-.01, p>.05$), with non-significant heterogeneity reported in the sample of effect sizes, $Q(4)=2.78, p>.05, I^2=11.96\%$.

Processing speed

Seven studies contributed effect sizes to a meta-analysis of genotype differences in processing speed. The average effect of carrying an $\epsilon 4$ allele was non-significant ($d=-.01$, $p>.05$). There was no significant heterogeneity in this sample of effect sizes, $Q(6)=7.15$, $p>.05$, $I^2=0\%$.

[Insert Table 3]

[Insert Figure 2]

Systematic review

Neuropsychological Assessment

The majority of studies examining the effect of *APOE* $\epsilon 4$ in mid-adulthood have chosen to administer a compilation of neuropsychological assessment measures. These studies report limited effects of *APOE* $\epsilon 4$ in mid-adulthood (e.g. Jorm et al., 2007; Marioni et al., 2016; Sager, Hermann, & La Rue, 2005; Shin et al., 2014; Zhao et al., 2005). Indeed, in a large community-based sample, the effect of *APOE* status was non-significant in both mid-adulthood (40-44 years), as well as groups aged 20-24 years and 60-64 years (Jorm et al., 2007), leading authors to conclude there are no preclinical effects of *APOE* genotype on cognition. Of interest, however, other studies suggest sample age is a key determinant in the expression of preclinical *APOE* $\epsilon 4$ effects. Age x *APOE* interactions were found both for scores on the Korean MMSE (Shin et al., 2014), and performance on measures of declarative memory and processing speed (Marioni et al., 2016). In both studies, detrimental effects of $\epsilon 4+$ status emerged when analyses isolated volunteers aged in the latter half of the 5th decade (55+ years and 60+ years respectively).

Mid-age studies investigating *APOE* differences across a broad range of neuropsychological measures typically observe $\epsilon 4+$ effects, when present, within a select domain. For example, in the research of Sager et al. (2005) $\epsilon 4+$ selectively showed worse performance on visuospatial processing tasks, driven by decrements on block design performance. In contrast, detrimental effects of $\epsilon 4+$ status were limited to female participants on tasks probing memory and semantic fluency (Zhao et al., 2005), whereas $\epsilon 4+$ advantages were reported in verbal fluency and language across the adult lifespan by Marioni et al., (2016). While the selectivity of effects agrees with reports of genotype effects in older adulthood (Small et al., 2004; Wisdom et al., 2011), failure to identify a consistent pattern of $\epsilon 4$ effects within a cognitive domain in mid-adulthood makes interpretation difficult.

Results within the domain of memory offer the clearest profile of cognitive differences in $\epsilon 4+$, with several studies associating possession of an $\epsilon 4$ allele with poorer memory performance (Caselli et al., 1999; Flory, Manuck, Ferrell, Ryan, & Muldoon, 2000; Goveas et al., 2013; Levy et al., 2004; Schultz et al., 2008). Attempts have been made to link differential memory performance with neural differences. In adults aged 44-65 years, $\epsilon 4+$ showed a trend of worse performance on the Rey Auditory Verbal Learning Test (AVLT) (Goveas et al., 2013). Performance on this task correlated with observed reductions in the functional connectivity of medial temporal lobe (MTL) circuits, as well as differential connectivity of the default mode network (Li et al., 2014; Goveas et al., 2013), offering a possible neurobiological basis of genotype differences. In addition, two studies report an altered BOLD response in $\epsilon 4+$ during episodic memory tasks, despite no detectable genotype difference in behavioural performance (Trachtenberg et al., 2012; Xu et al., 2009). Although this raises the question of how neural activations relate to cognition, identifying the neural basis of *APOE* differences will further mechanistic explanations of how *APOE* $\epsilon 4$ influences cognitive ageing.

Research has started to explore how carrying an *APOE* $\epsilon 4$ allele interacts with environmental factors in influencing performance on neuropsychological measures. Education was found to interact with *APOE* status in a cohort of adults aged 45-54 years, in that only $\epsilon 4+$ with no formal education showed cognitive advantages on a measure of global cognition compared to their $\epsilon 4-$ peers (Shin et al., 2014). In contrast, *APOE*, education and socio-economic status were reported to independently affect cognition (Zhao et al., 2005).

Considering cardiovascular health factors, an *APOE* x Blood Pressure interaction has been reported for cognition in mid-adulthood. Although there was no main effect of *APOE* status or systolic blood pressure on performance across 3 cognitive domains; episodic memory, visual memory or EF, in $\epsilon 4+$ only, high blood pressure was associated with worse episodic memory performance (Oberlin et al., 2015). High blood pressure was also found to enhance the negative association of *APOE* $\epsilon 4$ with processing speed and working memory (WM), as well as reduced white matter integrity in frontal regions (Bender & Raz, 2012). In both studies, the relationship between blood pressure and cognition was absent in the $\epsilon 4-$ group, suggesting cardiovascular health factors may exaggerate cognitive effects in $\epsilon 4+$.

Behavioural paradigms

Paradigms designed to detect subtle differences in cognition have predominantly been used to explore the sensitivity of executive abilities, including WM and attention, to *APOE* effects in mid-adulthood.

On a measure of covert attention, there was a non-significant effect of *APOE* genotype on overall performance, and on the ability to benefit from valid cues in mid-adulthood (Greenwood, Sunderland, Friz, & Parasuraman, 2000). $\epsilon 4+$, however, showed increased response time costs following an invalid cue, relative to $\epsilon 4-$ peers, interpreted as a

deficit in attentional disengagement. In contrast, a more recent study reported equivalent performance between genotype groups on this task (Evans et al., 2013; Evans, Dowell, Tabet, Tofts, King & Rusted, 2014). Control of visual attention was explored in an attentional scaling task (Greenwood et al., 2000; Greenwood, Lambert, Sunderland & Parasuraman, 2005a). The dynamic scaling task measures the ability to constrict one's attentional spotlight in response to top-down information cueing the spatial location of a target stimulus. $\epsilon 4+$ did not show the same benefit as their $\epsilon 4-$ peers in response times following more precise cues.

Executive attention was explored in a cross-sectional comparison of mid-age (aged 43-58) and young adults (aged 18-30) (Evans et al., 2013; 2014). On a measure of sustained attention, a trend of higher accuracy, coupled with slower reaction times, was found in mid-age $\epsilon 4+$ relative to their $\epsilon 4-$ peers. When compared to the data from the young group, the mid-age $\epsilon 4+$ group showed exaggerated age-related slowing. In comparison, a second study found no effect of *APOE* genotype on a similar task in adults aged 50+ (M=59 years) (Greenwood et al., 2000). A comparable pattern of results was seen on a prospective memory task, probing attentional monitoring and switching between goals. $\epsilon 4+$ demonstrated greater accuracy but slower response times on the prospective memory paradigm, suggestive of a speed-accuracy trade-off (Evans et al., 2013; 2014). Corresponding functional activations during this task indicated greater recruitment of frontal regions, but reduced recruitment of parietal and extrastriate visual regions in $\epsilon 4+$ relative to their $\epsilon 4-$ peers. Specifically, left inferior frontal gyrus activity correlated with prospective memory accuracy in $\epsilon 4+$ only, consistent with an early compensatory shift towards reliance on more frontal systems.

Genotype effects were explored using a selection of cognitive paradigms designed to probe the 3 components of executive function identified by Miyake et al. (2000): inhibition, switching and updating in WM (Velichkovsky, Roschina, & Selezneva, 2015). No genotype differences were recorded on either an anti-saccade inhibition measure, or two WM paradigms (*n*-back test, the operation span task). A non-significant effect of *APOE* $\epsilon 4$ status

on *n*-back performance has previously been reported in middle-aged adults (Chen et al., 2013; Yan, Wu, Chao, Chen, & Tseng, 2015). Both studies, however, reported a differential pattern of neural change in $\epsilon 4+$, with this group showing an absence of neural activation increases in correspondence to greater WM load (Chen et al., 2013; Yan et al., 2015). This was interpreted as $\epsilon 4+$ maximally recruiting processing resources at a lower level of load, which cannot be further increased under greater demands. Hence, it may be that on more demanding tasks, significant effects of carrying an $\epsilon 4$ allele may be observable. On the switching paradigm administered by Velichovsky et al., (2015), $\epsilon 4+$ showed significantly larger switching costs than their $\epsilon 4-$ counterparts.

Greenwood et al., (2005a) assessed spatial WM in adults, aged 41-85. Relative to $\epsilon 4-$, only homozygous $\epsilon 4+$ displayed a disadvantage on spatial WM tasks, driven by performance on trials placing the greatest load on spatial WM. In a further study of spatial WM, no genotype difference was seen in mid-age adults (Greenwood, Espeseth, Lin, Reinvang, & Parasuraman, 2014)

Longitudinal assessments

Several studies have explored how cognition changes longitudinally as a function of *APOE* genotype. Schultz et al. (2008) compared the cognitive test performance of army cadets in the 6th decade of life, to their scores on the same measure at age 20, and found $\epsilon 4+$ showed greater decline. Across a period of 6 years, relatively limited effects of *APOE* genotype were reported across a selection of cognitive domains (Zhao et al., 2005), with only semantic fluency being negatively associated with $\epsilon 4+$ status in females aged 40-49; this study reported no genotype differences in a slightly older sample (aged 50-59).

The dominant focus of longitudinal research has been establishing if $\epsilon 4+$ show a differential rate of memory change over time. Several studies suggest that $\epsilon 4+$ show

significantly greater memory decline from mid-adulthood (Caselli et al., 2009; Kozauer, Mielke, Chan, Rebok, & Lyketsos, 2008), with this effect isolated to delayed memory in two studies (Greenwood, Sunderland, Putnam, Levy, & Parasuraman, 2005b; Greenwood et al., 2014). Performance change across an average of 3.8 years was investigated for measures of memory (Jochimsen, Muller, van der Graaf, & Geerlings, 2012), with participants stratified by age. Of interest, it was found $\epsilon 4+$ aged 47-57 years showed improvements in recall performance, whilst $\epsilon 4+$ aged 58-67 years showed significant decline by the follow-up assessment. How change in memory is influenced by the interaction between *APOE* genotype, ethnicity and cardiovascular health has also been explored over a 6 year interval (Blair et al., 2005). Negative associations between $\epsilon 4+$ and memory change were small and limited to Caucasian adults. There was no interaction between cardiovascular health factors (diabetes, hypercholesterolemia, hypertension), *APOE* genotype and memory change.

Two papers found a non-significant effect of *APOE* genotype on change in executive abilities over time (Greenwood et al., 2014; Jochimsen et al., 2012). There is support, however, for the $\epsilon 4$ allele being associated with greater decline in processing speed (Blair et al., 2005; Caselli et al., 2011). In a group of Caucasian adults, $\epsilon 4+$ also diagnosed with hypercholesterolemia or diabetes showed increased decline on the digit-symbol substitution measure of processing speed (Blair et al., 2005). No *APOE* x Hypertension interaction was found for change in processing speed. Verbal fluency scores were maintained in both the Caucasian and Afro-American groups included in Blair et al. (2005).

Longitudinal measures (Greenwood et al., 2014) revealed no genotype difference across trials with relatively low WM demand. On trials incorporating a mismatch between encoded and target stimuli, and hence placing greater demand on WM resources, however, performance of $\epsilon 4+$ improved over 3 years, whilst performance of the $\epsilon 4-$ group remained stable. The observed practice effects in $\epsilon 4+$ were interpreted by the authors to represent

compensatory mechanisms during mid-adulthood, and as a result of the increased cognitive effort in this group, some $\epsilon 4+$ benefits were still observed.

Discussion

This review highlights the inconsistencies reported for *APOE* $\epsilon 4$ effects on cognition in mid-adulthood. Synthesising the results through meta-analyses, the effect of carrying an $\epsilon 4$ allele was non-significant across the 7 cognitive domains examined (global cognition, memory, executive ability, verbal fluency, language, visuospatial processing, and processing speed). Closer inspection of individual studies, however, indicates $\epsilon 4+$ effects may emerge under certain conditions, and when probed with measures designed to maximise sensitivity.

The results of the meta-analyses offer limited support for $\epsilon 4+$ showing cognitive differences in mid-adulthood; performance of $\epsilon 4+$ and $\epsilon 4-$ appears equivalent until the end of the 5th decade. This is not inconsistent with the antagonistic pleiotropy position whereby the $\epsilon 4$ allele has opposing effects on fitness across the lifespan (Han & Bondi, 2008), with mid-adulthood as a transition point between $\epsilon 4+$ behavioural advantages in youth switching to disadvantages in older adulthood.

When considering individual studies in more detail, the age range of participants is a likely factor in the inconsistency between study outcomes. Critically, existing research lacks a precise and consistent definition of mid-adulthood, reflected in the diverse and often broad age ranges of volunteers participating in the research reviewed here (see Table 1). For example, mid-adulthood was defined as 24-69 years in one study (Flory et al., 2000) and 41-85 years in another (Greenwood et al., 2005a). To draw conclusions of genotype effects at any precise window of the lifespan is difficult with such large age inclusion criteria, and the disparity in age groups may relate to the inconsistency of results presented. In cases where samples were stratified by age, Age x APOE interactions were reported, indicating emergence

of the detrimental effects of *APOE* $\epsilon 4$ in the latter half of the 5th decade (Jochemsen et al., 2012; Marioni et al., 2016; Shin et al., 2014). This highlights the importance of controlling for age. Age was not included as a moderator in the current meta-analyses due to the small number of studies in each domain, but this is certainly an important avenue for future research.

A key question for this review was whether process-specific cognitive measures show sensitivity to *APOE* genotype effects in mid-adulthood. Although the results of the meta-analyses failed to report a robust effect of $\epsilon 4+$ status on memory, looking across studies there is a relatively consistent pattern of emerging decrements in $\epsilon 4+$ performance (11/20 studies). Detrimental effects of $\epsilon 4+$ status on memory were also supported by longitudinal studies, suggesting this genotype group shows an accelerated trajectory of memory decline (Caselli et al., 2009; Greenwood et al., 2005; Greenwood et al., 2014; Kozauer et al., 2008). The sensitivity of memory to the effects of *APOE* $\epsilon 4$ from mid-adulthood is further supported by imaging evidence of genotype differences in MTL regions, implicating this region as a neural basis for behavioural changes (Goveas et al., 2013; Li et al., 2014). Memory is over-represented in studies probing the effects of *APOE*, and with more careful consideration of other cognitive domains, other effects may emerge.

It is important to consider that many of the study outcomes included in the meta-analyses were based on neuropsychological assessment performance. It may be that the preclinical effects of *APOE* $\epsilon 4$ are too subtle for detection with neuropsychological measures, more commonly used for the detection of clinically relevant symptoms. In support of this, studies using computerized paradigms designed to target specific cognitive processes report *APOE* $\epsilon 4$ differences in mid-adulthood within the domains of EF, attention and WM (Evans et al., 2013, 2014; Greenwood et al., 2000; 2005; 2014; Velichkovsky et al., 2015). These domains have also been linked to $\epsilon 4+$ cognitive advantages in early adulthood (Marchant et al., 2010; Rusted et al., 2013; Taylor et al., 2016), and so may show early sensitivity to

genotype effects. Future research should focus on specific cognitive processes in order to establish the pattern of age-related change more clearly. Identifying replicable cognitive markers of those at heightened risk of poor cognitive ageing would make a substantial contribution to the development of early intervention strategies, independently and in association with the study of biomarkers and additional risk factors for dementia.

An additional methodological issue is the role of individual differences in moderating the effects of *APOE*. Several studies attempt to control for differences in ethnicity, education, socio-economic status (SES), and health factors; however, these factors are not uniformly included. Investigation of how these factors interact with *APOE* $\epsilon 4$ to alter the initial stages of ageing is limited to date. Although methodological shortcomings contribute to the inconsistency of findings, it is important to recognise that mid-age itself will play an important role. Mid-age brings with it other risk factors for poor cognitive ageing (e.g. hypertension, high cholesterol and diabetes (Atzmon et al., 2002; Köhler et al., 2014; van Exel et al., 2002; Whitmer, Sidney, Selby, Johnston, & Yaffe, 2005), and interactions between vascular health, APOE and cognition are reported (de Frias, Schaie, & Willis, 2014; Peila et al., 2001; Puttonen, Elovainio, Kivimäki, Lehtimäki, & Keltikangas-Järvinen, 2003; Zade et al., 2010). Current behavioural research is neither considering the potential modifying effects of wider risk factors nor adequately controlling for them, though they undoubtedly contribute to the cognitive ageing trajectory (Herrup, 2010). One account for the role of *APOE* $\epsilon 4$ in cognitive ageing is that this allele represents a genetic susceptibility, increasing vulnerability to both detrimental and protective factors in cognitive ageing (Wirth, Villeneuve, La Joie, Marks, & Jagust, 2014). Mid-adulthood represents a period of the lifespan where $\epsilon 4+$ are particularly susceptible to cognitive insults and benefits, and this underlines the need to consider the cognitive profile of $\epsilon 4+$ in relation to other potential modulators for cognitive health when establishing the preclinical effects of this gene.

Conclusions

It remains difficult to untangle the effects of *APOE* $\epsilon 4$ on cognition in mid-adulthood; methodological issues including imprecise criteria for age of volunteers and differential sensitivity of the measures used make it hard to form concrete conclusions. Results reviewed here suggest the cognitive performance of $\epsilon 4+$ in mid-adulthood is broadly comparable with their $\epsilon 4-$ counterparts. Subtle differences in memory and executive abilities are reported, however, where more sensitive measures of cognition are used, suggestive of the beginnings of a differential ageing trajectory in $\epsilon 4+$. Future research should focus on administering cognitive paradigms specifically chosen for their ability to sensitively measure the more nuanced processes in each particular domain, rather than relying on assessment measures more traditional of clinical settings. Since mid-age is a time when the trajectory of cognitive ageing will be influenced by multiple factors, these must also be incorporated when modelling the effects of *APOE* $\epsilon 4$ across the lifespan. Through the consideration of these factors in future study design reliable cognitive markers for exposing accelerated cognitive ageing in mid-adulthood may be developed.

Disclosure statement

There are no conflicts of interest to disclose.

References

- Alexander, D. M., Williams, L. M., Gatt, J. M., Dobson-Stone, C., Kuan, S. a, Todd, E. G., ... Gordon, E. (2007). The contribution of apolipoprotein E alleles on cognitive performance and dynamic neural activity over six decades. *Biological Psychology*, 75(3), 229–38. doi:10.1016/j.biopsycho.2007.03.001
- Alzheimer's society. (2016). *Alzheimersorguk*. Retrieved 5 April, 2016, from https://www.alzheimers.org.uk/site/scripts/documents_info.php?documentID=341
- Atzmon, G., Gabriely, I., Greiner, W., Davidson, D., Schechter, C., & Barzilai, N. (2002). Plasma HDL Levels Highly Correlate With Cognitive Function in Exceptional Longevity. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, 57(11), 712–715. doi:10.1093/gerona/57.11.M712
- Bender, A. R., & Raz, N. (2012). Age-related differences in memory and executive functions in healthy APOE ε4 carriers: The contribution of individual differences in prefrontal volumes and systolic blood pressure. *Neuropsychologia*, 50(5), 704–714. doi:10.1016/j.neuropsychologia.2011.12.025
- Blair, C. K., Folsom, a R., Knopman, D. S., Bray, M. S., Mosley, T. H., & Boerwinkle, E. (2005). APOE genotype and cognitive decline in a middle-aged cohort. *Neurology*, 64(2), 268–76. doi:10.1212/01.WNL.0000149643.91367.8A
- Borenstein, M., Hedges, L., Higgins, J., & Rothstein, H. (2009). Complex Data Structures. *Introduction to Meta-Analysis*. John Wiley & Sons Ltd., West Sussex, UK, 215–245.
- Bunce, D., Anstey, K. J., Burns, R., Christensen, H., & Eastal, S. (2011). Does possession of apolipoprotein E ε4 benefit cognitive function in healthy young adults? *Neuropsychologia*, 49(7), 1693–1697. doi:10.1016/j.neuropsychologia.2011.02.042
- Bunce, D., Bielak, A. a M., Anstey, K. J., Cherbuin, N., Batterham, P. J., & Eastal, S. (2014). APOE genotype and cognitive change in young, middle-aged, and older adults living in the community. *The Journals of Gerontology. Series A, Biological Sciences and Medical Sciences*, 69(4), 379–386. doi:10.1093/gerona/glt103
- Bunce, D., Kivipelto, M., & Wahlin, A. (2004). Utilization of cognitive support in episodic free recall as a function of apolipoprotein E and vitamin B12 or folate among adults aged 75 years and older. *Neuropsychology*, 18(2), 362–70. doi:10.1037/0894-4105.18.2.362
- Caselli, R. J., Chen, K., Lee, W., Alexander, G. E., & Reiman, E. M. (2008). Correlating cerebral hypometabolism with future memory decline in subsequent converters to amnesic pre-mild cognitive impairment. *Archives of Neurology*, 65(9), 1231–1236.
- Caselli, R. J., Chen, K., Locke, D. E. C., Lee, W., Roontiva, A., Bandy, D., ... Reiman, E. M. (2014). Subjective cognitive decline: self and informant comparisons. *Alzheimer's & Dementia*, 10(1), 93–98.
- Caselli, R. J., Dueck, A. C., Locke, D. E. C., Hoffman-Snyder, C. R., Woodruff, B. K., Rapsak, S. Z., & Reiman, E. M. (2011). Longitudinal modeling of frontal cognition in APOE ε4 homozygotes, heterozygotes, and noncarriers. *Neurology*, 76(16), 1383–1388. doi:10.1212/WNL.0b013e3182167147
- Caselli, R. J., Dueck, A. C., Osborne, D., Sabbagh, M. N., Connor, D. J., Ahern, G. L., ... Reiman, E. M. (2009). Longitudinal modeling of age-related memory decline and the APOE epsilon4 effect. *The New England Journal of Medicine*, 361, 255–263. doi:10.1016/S0084-3954(09)79603-4

- Caselli, R. J., Graff-Radford, N. R., Reiman, E. M., Weaver, A., Osborne, D., Lucas, J., ... Thibodeau, S. N. (1999). Preclinical memory decline in cognitively normal apolipoprotein E- ϵ 4 homozygotes. *Neurology*, 53(1), 201.
- Chen, C.-J., Chen, C.-C., Wu, D., Chi, N.-F., Chen, P.-C., Liao, Y.-P., ... Hu, C.-J. (2013). Effects of the apolipoprotein E ϵ 4 allele on functional MRI during n-back working memory tasks in healthy middle-aged adults. *American Journal of Neuroradiology*, 34(6), 1197–202. doi:10.3174/ajnr.A3369
- Corder, E.H., Saunders, A.M., Strittmatter, W. J., Schmechel, D.E., Gaskell, P.C., Small, G...&Pericak-Vance, M. . (1993). Gene does of apolipoprotein E type 4 allele and the risk of Alzheimer's disease in late onset families. *Science*, 261(5123), 921–923.
- DeCoster, J. (2009). Meta-Analysis Notes. Retrieved 07/28/2016 from <http://www.stat-help.com/notes.html>
- Deeny, S. P., Poeppel, D., Zimmerman, J. B., Roth, S. M., Brandauer, J., Witkowski, S., ... Brandt, J. (2008). Exercise, APOE, and working memory: MEG and behavioral evidence for benefit of exercise in epsilon4 carriers. *Biological Psychology*, 78(2), 179–187.
- Donix, M., Burggren, A. C., Suthana, N. A., Siddarth, P., Ekstrom, A. D., Krupa, A. K., ... Bookheimer, S. Y. (2010). Family history of Alzheimer's disease and hippocampal structure in healthy people. *American Journal of Psychiatry*, 167(11), 1399–1406. doi:10.1176/appi.ajp.2010.09111575
- Evans, S., Dowell, N. G., Tabet, N., Tofts, P. S., King, S. L., Gray, M., & Rusted, J. M. (2013). Nicotine effects on attentional reorienting in mid-age adults, and interactions with apolipoprotein E status. *Journal of Psychopharmacology (Oxford, England)*, 27(11), 1007–14. doi:10.1177/0269881113499828
- Evans, S., Dowell, N. G., Tabet, N., Tofts, P. S., King, S. L., & Rusted, J. M. (2014). Cognitive and neural signatures of the APOE E4 allele in mid-aged adults. *Neurobiology of Aging*, 35(7), 1615–1623. doi:10.1016/j.neurobiolaging.2014.01.145
- Farrer, L. A., Cupples, L. A., Haines, J. L., Hyman, B., Kukull, W. a, Mayeux, R., ... van Duijn, C. M. (1997). Effects of age, sex, and ethnicity on the association between apolipoprotein E genotype and Alzheimer disease. A meta-analysis. APOE and Alzheimer Disease Meta Analysis Consortium. *JAMA : The Journal of the American Medical Association*, 278(16), 1349–1356. doi:10.1001/jama.1997.03550160069041
- Flory, J. D., Manuck, S. B., Ferrell, R. E., Ryan, C. M., & Muldoon, M. F. (2000). Memory Performance and the Apolipoprotein E Polymorphism in a Community Sample of Middle-Aged Adults. *American Journal of Medical Genetics*, 96(6), 707–711. doi:10.1002/1096-8628(20001204)96:6<707::AID-AJMG1>3.0.CO;2-V
- Frias, C. M. De, Schaie, K. W., & Willis, S. L. (2014). Hypertension Moderates the Effect of APOE on 21-Year Cognitive Trajectories. *Psychology and Aging*, 29(2), 431–439. doi:10.1037/a0036828
- Goveas, J. S., Xie, C., Chen, G., Li, W., Ward, B. D., Franczak, M. B., ... Li, S.-J. (2013). Functional network endophenotypes unravel the effects of apolipoprotein E epsilon 4 in middle-aged adults. *PloS One*, 8(2), e55902. doi:10.1371/journal.pone.0055902
- Greenwood, P. M., Sunderland, T., Friz, J. L., & Parasuraman, R. (2000). Genetics and visual attention: Selective deficits in healthy adult carriers of the ϵ 4 allele of the apolipoprotein E gene. *Proceedings of the National Academy of Sciences*, 97(21), 11661–11666.
- Greenwood, P. M., Lambert, C Sunderland, T, Parasuraman, R. (2005a). Effects of

- Apolipoprotein E Genotype on Spatial Attention, Working Memory, and their interaction in Healthy, Middle-Aged Adults: Results from the National Institute of Mental Health's BIOCARD study. *Neuropsychology*, 19(2), 199–211.
- Greenwood, P. M., Espeseth, T., Lin, M.-K., Reinvang, I., & Parasuraman, R. (2014). Longitudinal change in working memory as a function of APOE genotype in midlife and old age. *Scandinavian Journal of Psychology*, 55(3), 268–77. doi:10.1111/sjop.12123
- Greenwood, P. M., Sunderland, T., Putnam, K., Levy, J., & Parasuraman, R. (2005b). Scaling of visuospatial attention undergoes differential longitudinal change as a function of APOE genotype prior to old age: Results from the NIMH BIOCARD Study. *Neuropsychology*, 19(6), 830–40. doi:10.1037/0894-4105.19.6.830
- Han, S. D., & Bondi, M. W. (2008). Revision of the apolipoprotein E compensatory mechanism recruitment hypothesis. *Alzheimer's & Dementia : The Journal of the Alzheimer's Association*, 4(4), 251–254. doi:10.1016/j.jalz.2008.02.006
- Han, S. D., Drake, A. I., Cessante, L. M., Jak, A. J., Houston, W. S., Delis, D. C., ... Bondi, M. W. (2007). Apolipoprotein E and traumatic brain injury in a military population: evidence of a neuropsychological compensatory mechanism? *Journal of Neurology, Neurosurgery, and Psychiatry*, 78(10), 1103–8. doi:10.1136/jnnp.2006.108183
- Herrup, K. (2010). Reimagining Alzheimer's Disease--An Age-Based Hypothesis. *Journal of Neuroscience*, 30(50), 16755–16762. doi:10.1523/JNEUROSCI.4521-10.2010
- Hubacek, J. A., Pitha, J., Škodová, Z., Adámková, V., Lánská, V., & Poledne, R. (2001). A Possible Role of Apolipoprotein E Polymorphism in Predisposition to Higher Education. *Neuropsychobiology*, 43(3), 200–203. doi:10.1159/000054890
- Ihle, A., Bunce, D., & Kliegel, M. (2012). APOE ε4 and cognitive function in early life: a meta-analysis. *Neuropsychology*, 26(3), 267–277. doi:10.1037/a0026769
- Jochemsen, H. M., Muller, M., van der Graaf, Y., & Geerlings, M. I. (2012). APOE ε4 differentially influences change in memory performance depending on age. The SMART-MR study. *Neurobiology of Aging*, 33(4), 832.e15–22. doi:10.1016/j.neurobiolaging.2011.07.016
- Jorm, A. F., Mather, K. a, Butterworth, P., Anstey, K. J., Christensen, H., & Easteal, S. (2007). APOE genotype and cognitive functioning in a large age-stratified population sample. *Neuropsychology*, 21(1), 1–8. doi:10.1037/0894-4105.21.1.1
- Köhler, S., Baars, M. A. E., Spauwen, P., Schievink, S., Verhey, F. R. J., & van Boxtel, M. J. P. (2014). Temporal evolution of cognitive changes in incident hypertension: prospective cohort study across the adult age span. *Hypertension*, 63(2), 245–51. doi:10.1161/HYPERTENSIONAHA.113.02096
- Kozauer, N. A., Mielke, M. M., Chan, G. K. C., Rebok, G. W., & Lyketsos, C. G. (2008). Apolipoprotein E genotype and lifetime cognitive decline. *International Psychogeriatrics*, 20(01), 109–123. doi:10.1017/S104161020700587X
- Langbaum, J. B. S., Chen, K., Caselli, R. J., Lee, W., Reschke, C., Bandy, D., ... Reeder, S. A. (2010). Hypometabolism in Alzheimer-affected brain regions in cognitively healthy Latino individuals carrying the apolipoprotein E ε4 allele. *Archives of Neurology*, 67(4), 462–468.
- Levy, J. A., Bergeson, J., Putnam, K., Rosen, V., Cohen, R., Lalonde, F., ... Sunderland, T. (2004). Context-specific memory and apolipoprotein E (ApoE) epsilon 4: cognitive evidence from the NIMH prospective study of risk for Alzheimer's disease. *Journal of the International Neuropsychological Society*, 10(3), 362–370. doi:10.1017/S1355617704103044

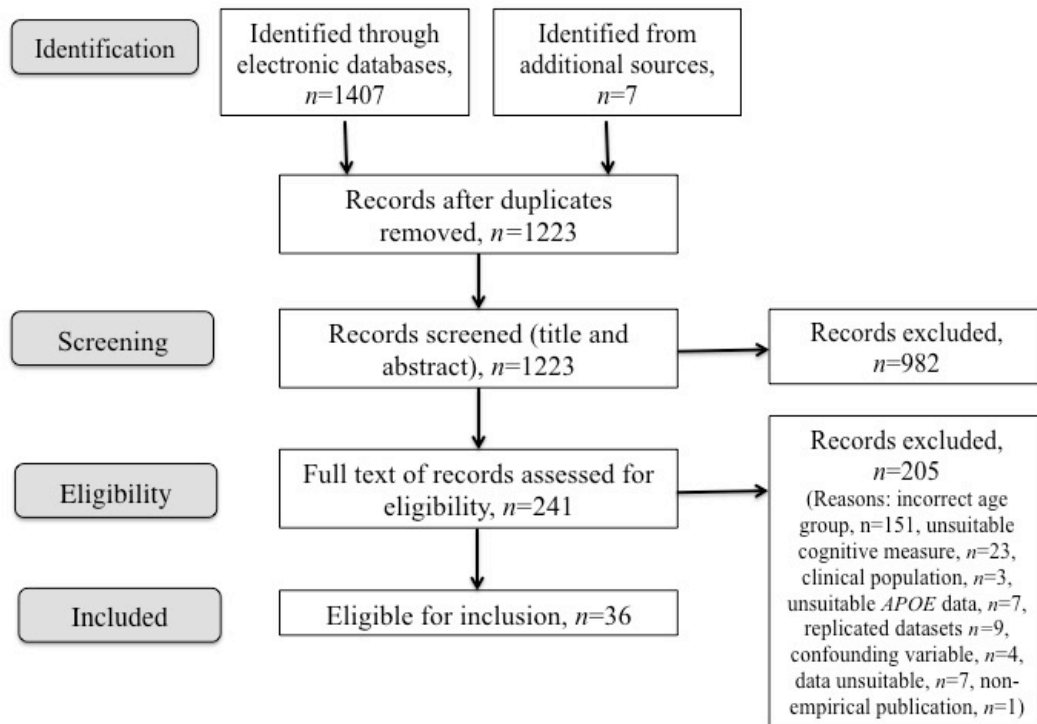
- Li, W., Antuono, P. G., Xie, C., Chen, G., Jones, J. L., Ward, B. D., ... Li, S.-J. (2014). Aberrant functional connectivity in Papez circuit correlates with memory performance in cognitively intact middle-aged APOE4 carriers. *Cortex*, 57, 167–76. doi:10.1016/j.cortex.2014.04.006
- Mahley, R. W. (1988). Apolipoprotein E : cholesterol transport protein with expanding role in cell biology. *Science*, 240(4852), 622–630.
- Marchant, N. L., King, S. L., Tabet, N., & Rusted, J. M. (2010). Positive effects of cholinergic stimulation favor young APOE epsilon4 carriers. *Neuropsychopharmacology*, 35(5), 1090–6. doi:10.1038/npp.2009.214
- Marioni, R. E., Campbell, A., Scotland, G., Hayward, C., Porteous, D. J., & Deary, I. J. (2016). Differential effects of the APOE ε4 allele on different domains of cognitive ability across the life-course. *European Journal of Human Genetics*, 24, 919–923. doi:10.1038/ejhg.2015.210
- Miyake, A., Friedman, N. P., Emerson, M. J., Witzki, a H., Howerter, A., & Wager, T. D. (2000). The unity and diversity of executive functions and their contributions to complex “Frontal Lobe” tasks: a latent variable analysis. *Cognitive Psychology*, 41(1), 49–100. doi:10.1006/cogp.1999.0734
- Mondadori, C. R. a, de Quervain, D. J.-F., Buchmann, A., Mustovic, H., Wollmer, M. A., Schmidt, C. F., ... Henke, K. (2007). Better memory and neural efficiency in young apolipoprotein E epsilon4 carriers. *Cerebral Cortex*, 17(8), 1934–47. doi:10.1093/cercor/bhl103
- Nichols, L. M., Masdeu, J. C., Mattay, V. S., Kohn, P., Emery, M., Sambataro, F., ... Weinberger, D. R. (2012). Interactive effect of apolipoprotein e genotype and age on hippocampal activation during memory processing in healthy adults. *Archives of General Psychiatry*, 69(8), 804–813.
- Oberlin, L. E., Manuck, S. B., Gianaros, P. J., Ferrell, R. E., Muldoon, M. F., Jennings, J. R., ... Erickson, K. I. (2015). Blood Pressure Interacts With APOE ε4 to Predict Memory Performance in a Midlife Sample. *Neuropsychology*, 29(5), 693–702. doi:neu0000177
- Panizzon, M. S., Hauger, R., Xian, H., Vuoksimaa, E., Spoon, K. M., Mendoza, S. P., ... Franz, C. E. (2014). Interaction of APOE genotype and testosterone on episodic memory in middle-aged men. *Neurobiology of Aging*, 35(7), 1778.e1–1778.e8. doi:10.1016/j.neurobiolaging.2013.12.025
- Patel, K. T., Stevens, M. C., Pearlson, G. D., Winkler, A. M., Hawkins, K. A., Skudlarski, P., & Bauer, L. O. (2013). Default mode network activity and white matter integrity in healthy middle-aged ApoE4 carriers. *Brain Imaging and Behavior*, 7(1), 60–67. doi:10.1007/s11682-012-9187-y
- Peila, R., White, L. R., Petrovich, H., Masaki, K., Ross, G. W., Havlik, R. J., & Launer, L. J. (2001). Joint effect of the APOE gene and midlife systolic blood pressure on late-life cognitive impairment: the Honolulu-Asia aging study. *Stroke*, 32(12), 2882–2889. doi:10.1161/hs1201.100392
- Protas, H. D., Chen, K., Langbaum, J. B. S., Fleisher, A. S., Alexander, G. E., Lee, W., ... Reiman, E. M. (2013). Posterior cingulate glucose metabolism, hippocampal glucose metabolism, and hippocampal volume in cognitively normal, late-middle-aged persons at 3 levels of genetic risk for Alzheimer disease. *JAMA Neurology*, 70(3), 320–5. doi:10.1001/2013.jamaneurol.286
- Puttonen, S., Elovainio, M., Kivimäki, M., Lehtimäki, T., & Keltikangas-Järvinen, L. (2003). The Combined Effects of Apolipoprotein E Polymorphism and Low-Density Lipoprotein Cholesterol on Cognitive Performance in Young Adults.

- Neuropsychobiology*, 48(1), 35–40. doi:10.1159/000071827
- Ready, R. E., Baran, B., Chaudhry, M., Schatz, K., Gordon, J., & Spencer, R. M. C. (2011). Apolipoprotein E-ε4, processing speed, and white matter volume in a genetically enriched sample of midlife adults. *American Journal of Alzheimer's Disease and Other Dementias*, 26(6), 463–8. doi:10.1177/1533317511421921
- Rusted, J. M., Evans, S. L., King, S. L., Dowell, N., Tabet, N., & Tofts, P. S. (2013). APOE ε4 polymorphism in young adults is associated with improved attention and indexed by distinct neural signatures. *Neuroimage*, 65, 364–373. doi:10.1016/j.neuroimage.2012.10.010
- Sager, M., Hermann, B., & La Rue, A. (2005). Middle-aged children of persons with Alzheimer's disease: APOE genotypes and cognitive function in the Wisconsin Registry for Alzheimer's Prevention. *Journal of Geriatric Psychiatry and Neurology*, 18(4), 245–9. doi:10.1177/0891988705281882
- Schultz, M. R., Lyons, M. J., Franz, C. E., Grant, M. D., Boake, C., Jacobson, K. C., ... Kremen, W. S. (2008). Apolipoprotein E genotype and memory in the sixth decade of life. *Neurology*, 70(19 Pt 2), 1771–7. doi:10.1212/01.wnl.0000286941.74372.cc
- Shin, M. H., Kweon, S. S., Choi, J. S., Lee, Y. H., Nam, H. S., Park, K. S., ... Jeong, S. K. (2014). The effect of an APOE polymorphism on cognitive function depends on age. *Journal of Neurology*, 261, 66–72. doi:10.1007/s00415-013-7157-y
- Small, B. J., Rosnick, C. B., Fratiglioni, L., & Bäckman, L. (2004). Apolipoprotein E and cognitive performance: a meta-analysis. *Psychology and Aging*, 19(4), 592–600. doi:10.1037/0882-7974.19.4.592
- Sunderland, T., Mirza, N., Putnam, K. T., Linker, G., Bhupali, D., Durham, R., ... Cohen, R. M. (2004). Cerebrospinal fluid ??-amyloid 1-42 and tau in control subjects at risk for Alzheimer's disease: The effect of APOE ??4 allele. *Biological Psychiatry*, 56(9), 670–676. doi:10.1016/j.biopsych.2004.07.021
- Taylor, W. D., Boyd, B., Turner, R., McQuoid, D. R., Ashley-Koch, A., MacFall, J. R., ... Potter, G. G. (2016). APOE ε4 associated with preserved executive function performance and maintenance of temporal and cingulate brain volumes in younger adults. *Brain Imaging and Behavior*. doi:10.1007/s11682-016-9522-9
- Trachtenberg, A. J., Filippini, N., Cheeseman, J., Duff, E. P., Neville, M. J., Ebmeier, K. P., ... Mackay, C. E. (2012). The effects of APOE on brain activity do not simply reflect the risk of Alzheimer's disease. *Neurobiology of Aging*, 33(3), 618.e1–618.e13. doi:10.1016/j.neurobiolaging.2010.11.011
- van Exel, E., de Craen, A. J. M., Gussekloo, J., Houx, P., Bootsma-van der Wiel, A., Macfarlane, P. W., ... Westendorp, R. G. J. (2002). Association between high-density lipoprotein and cognitive impairment in the oldest old. *Annals of Neurology*, 51(6), 716–21. doi:10.1002/ana.10220
- Velichkovsky, B. B., Roschina, I. F., & Selezneva, N. D. (2015). Cognitive control and memory in healthy ApoE-ε4 carriers with a family history of Alzheimer's disease. *Psychology in Russia: State of the Art*, 8(1), 4–13. doi:10.11621/pir.2015.0101
- Walhovd, K. B., Fjell, A. M., & Espeseth, T. (2014). Cognitive decline and brain pathology in aging--need for a dimensional, lifespan and systems vulnerability view. *Scandinavian Journal of Psychology*, 55(3), 244–54. doi:10.1111/sjop.12120
- Whitmer, R. A., Sidney, S., Selby, J., Johnston, S. C., & Yaffe, K. (2005). Midlife cardiovascular risk factors and risk of dementia in late life. *Neurology*, 64(2), 277–281. doi:10.1212/01.WNL.0000149519.47454.F2

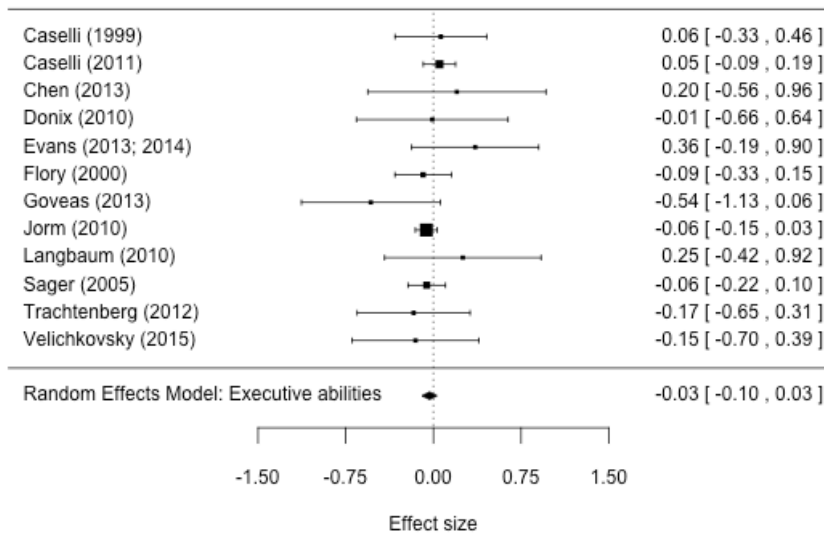
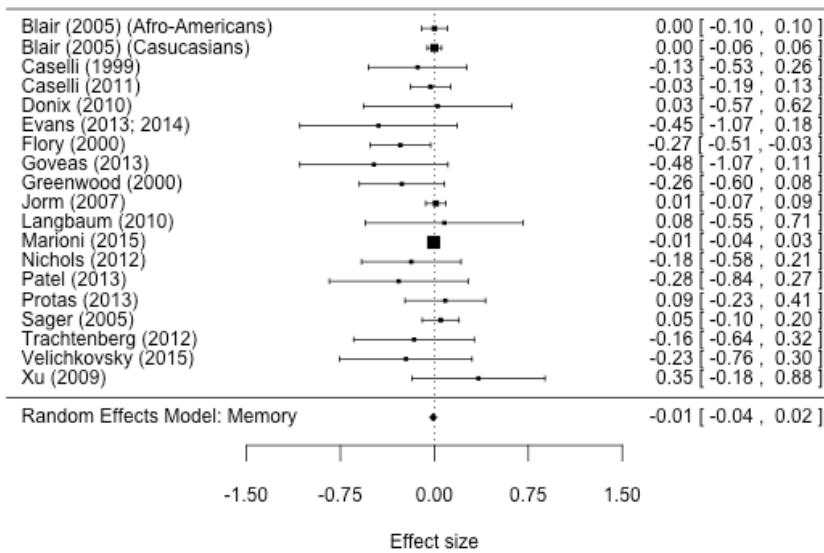
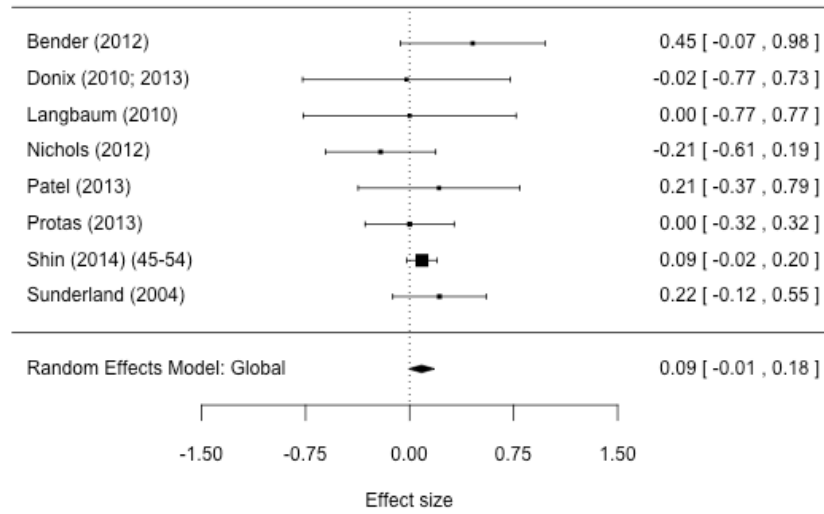
- Wirth, M., Villeneuve, S., La Joie, R., Marks, S. M., & Jagust, W. J. (2014). Gene-environment interactions: lifetime cognitive activity, APOE genotype, and β -amyloid burden. *The Journal of Neuroscience : The Official Journal of the Society for Neuroscience*, 34(25), 8612–7. doi:10.1523/JNEUROSCI.4612-13.2014
- Wisdom, N. M., Callahan, J. L., & Hawkins, K. A. (2011). The effects of apolipoprotein E on non-impaired cognitive functioning: a meta-analysis. *Neurobiology of Aging*, 32(1), 63–74. doi:10.1016/j.neurobiolaging.2009.02.003
- Xu, G., McLaren, D. G., Ries, M. L., Fitzgerald, M. E., Bendlin, B. B., Rowley, H. a, ... Johnson, S. C. (2009). The influence of parental history of Alzheimer's disease and apolipoprotein E epsilon4 on the BOLD signal during recognition memory. *Brain*, 132(Pt 2), 383–91. doi:10.1093/brain/awn254
- Yan, F.-X., Wu, C. W., Chao, Y.-P., Chen, C.-J., & Tseng, Y.-C. (2015). APOE- ϵ 4 Allele Altered the Rest-Stimulus Interactions in Healthy Middle-Aged Adults. *PloS One*, 10(6), e0128442. doi:10.1371/journal.pone.0128442
- Yu, Y. W., Lin, C. H., Chen, S. P., Hong, C. J., & Tsai, S. J. (2000). Intelligence and event-related potentials for young female human volunteer apolipoprotein E epsilon4 and non-epsilon4 carriers. *Neuroscience Letters*, 294, 179–181. doi:S030439400001569X [pii]
- Zade, D., Beiser, A., McGlinchey, R., Au, R., Seshadri, S., Palumbo, C., ... Milberg, W. (2010). Interactive Effects of Apolipoprotein E Type 4 Genotype and Cerebrovascular Risk on Neuropsychological Performance and Structural Brain Changes. *Journal of Stroke and Cerebrovascular Diseases*, 19(4), 261–268. doi:10.1016/j.jstrokecerebrovasdis.2009.05.001
- Zhao, J. H., Brunner, E. J., Kumari, M., Singh-Manoux, a., Hawe, E., Talmud, P. J., ... Humphries, S. E. (2005). APOE polymorphism, socioeconomic status and cognitive function in mid-life. The Whitehall II longitudinal study. *Social Psychiatry and Psychiatric Epidemiology*, 40, 557–563. doi:10.1007/s00127-005-0925-y
- Zuelsdorff, M. L., Engelman, C. D., Friedman, E. M., Kosciak, R. L., Jonaitis, E. M., La Rue, A., & Sager, M. A. (2013). Stressful events, social support, and cognitive function in middle-aged adults with a family history of Alzheimer's disease. *Journal of Aging and Health*, 0898264313498416.

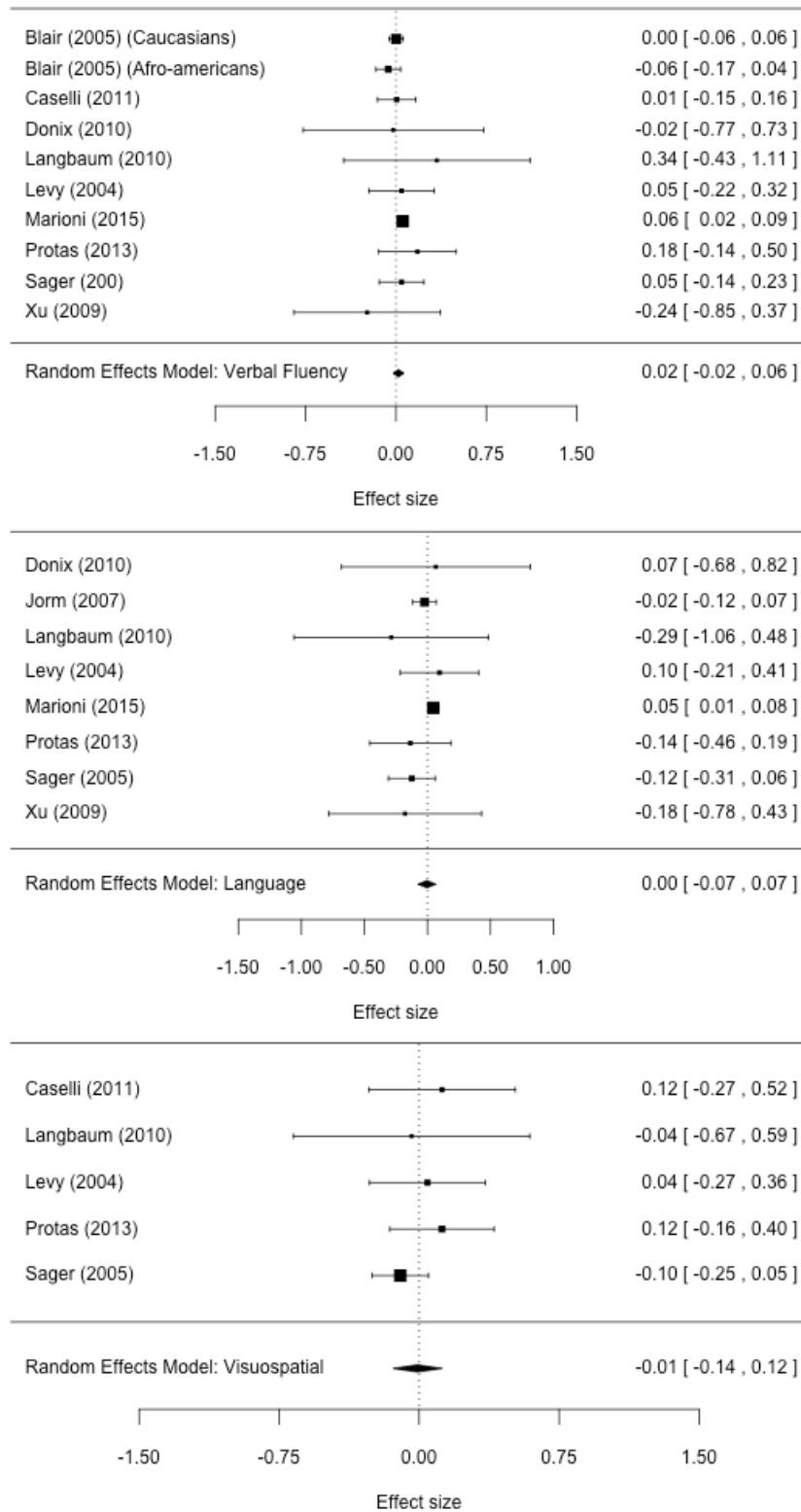
Figures and Tables

1.



2.





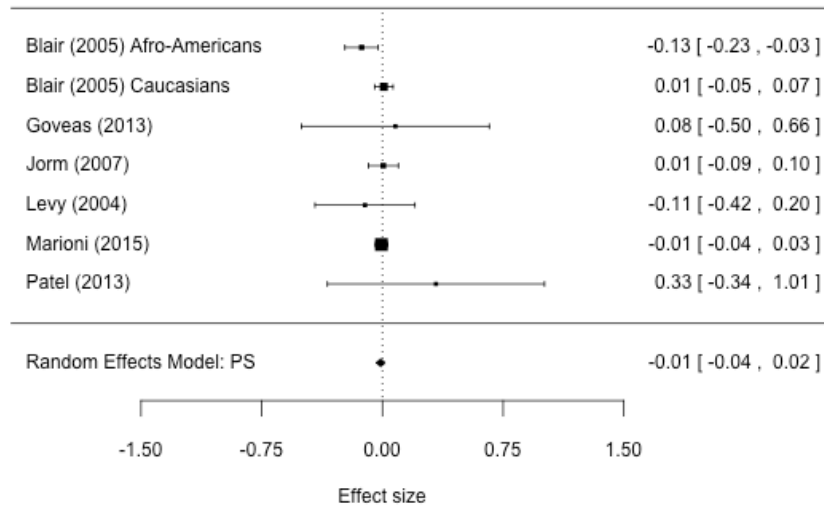


Figure Captions

Figure 1. Flow chart of study selection process for review of APOE effects in mid-adulthood.

Figure 2. Forest plots of weighted effect sizes by cognitive domain. For each study, effect size is reported as Hedge's d [95% CI], where a positive effect size represents greater performance by the $\epsilon 4+$ group.